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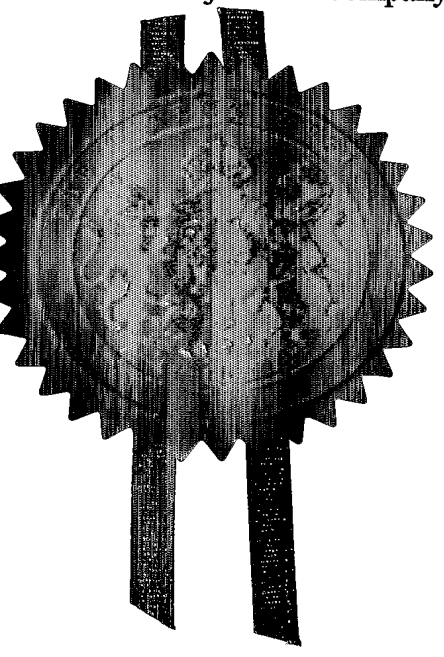

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Patents ADP number *(if you know it)* — 03969284001

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4. Title of the invention — Tunable Segmented Polyacetal

5. Name of your agent *(if you have one)* — John Hobbs

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Tunable segmented polyacetal

The present invention relates to polymer compositions and artefacts made therefrom. In particular the present invention relates to bioerodible polymers having high mechanical strength and their use for the manufacture of load bearing medical devices suitable for implantation within the body.

The degradation characteristics of the aliphatic polyesters are not ideal. Polyglycolic acid and copolymers with a high glycolic acid component (e.g. polyglyconate) lose strength rapidly (typically in around 4 weeks). Most healing processes (e.g. fracture repair, bone healing etc) can take longer than this (typically 6 to12 weeks). Therefore implants made of these polymers do not provide mechanical support over the full duration of healing. For these polymers mass loss generally occurs after about 1 –1.5 years. The release of glycolic acid breakdown products has been linked to inflammatory reactions.

In contrast, polymers based on poly(L-lactide) (PLLA) retain their mechanical properties for much longer (typically 6-12 months) which means that they can provide mechanical support throughout the healing process. However, PLLA does not undergo complete mass loss for 3-5 years. This means that the device cannot be replaced by tissue until long after it has ceased to provide any function, if at all. As with PGA, the breakdown products released on degradation are acidic and can lead to an inflammatory response.

One way which has been attempted to create more optimal degradation rates is through the use of copolymers of lactic acid and glycolic acid (PLGA), or copolymers of L-lactic acid and D-lactic acid (PDLLA). The degradation times for these polymers are between those of PLLA and PGA However, these polymers are amorphous and have poorer mechanical properties than PGA and PLLA. Also, like PLLA and PGA they degrade by bulk hydrolysis so that significant mass loss and space generation for tissue ingrowth occurs long after loss of mechanical strength.

A further problem with materials such as PLLA and PGA is that they are brittle and implants made from them can be prone to breaking to the forces exerted on them during insertion. One way that this has been addressed is to copolymerise the PLLA or PGA with a rubber-like polymer such as poly(trimethylene carbonate). This improves the toughness of the polymer but such materials still suffer the same problems of degradation profile as PLLA and PGA.

Another biodegradable polymer which has been used is polycaprolactone (PCL). This polymer melts at around 60 °C so can be delivered to the body in a molten form after which it will set to form an implant in-situ. However, polycaprolactone has a very low degradation rate so that mass loss in the body takes over 3 years.

It is therefore an objective of the present invention to provide a biodegradable polymer that has optimum strength and degradation characteristics for procedures where biodegradable polymers are implanted.

According to the present invention there is provided a biodegradable segmented block copolymer comprising polyol residues having a molecular weight (Mn) of at least 4000 Daltons connected by acetal linkages.

Said residues are hereinafter referred to as "strength components".

According to a first embodiment of the present invention and the acetal linkages comprise polyacetal residues (A schematic representation of polymers in accordance with this embodiment of the invention is shown in Figure 1 of the accompanying drawings).

In one form of said first embodiment the polyacetal residues may comprise enzyme degradable polyacetal/diamino acid ester blocks (as illustrated Figure 2 of the accompanying drawings).

Alternatively and thepolyacetal residues may contain an incorporated bioactive diol (as illustrated in Figure 3 of the accompanying drawings).

The polyacetal residues may contain both enzyme degradable polyacetal/diamino acid ester blocks and incorporated bioactive agent (as illustrated in Figure 4 of the accompanying drawings).

According to a further embodiment of the present invention the segmented block copolymers of the invention may be blended with other polymeric or ceramic materials

The strength components of the present invention are polyols of at least 4000 Daltons or more preferably between 4000 and 20000 daltons. Suitable polyols may comprise polyesters such as homo- or copolymers of polycaprolactone (PCL), polylactic acid (PLA, L and D forms), polyglycolic acid (PGA) or polydioxanone. Other suitable polyols may comprise degradable aliphatic or aromatic esters, degradable carbonates such as dimethyl trimethylene carbonate (DMTMC), polyamides, polyurethanes and the like.

The amino acid diester/acetal blocks are aptly enzyme degradable blocks linked by acetal links and are based on amino acids. Said blocks can be produced by the reaction of amino acids with amines, acids, alcohols or isocynates groups to give degradable amino acid containing units which can be converted into the corresponding dihydroxy terminated blocks i.e. a diamino terminated amino acid block can be reacted with caprolactone to yield a dihydroxy terminated enzyme degradable amino acid block.

The polyacetal blocks are hydrolytically degradable blocks which may contain aromatic, aliphatic and/or alicyclic groups. The blocks will typically be formed by the reaction of divinyl ethers with alcohols. Typical examples are cyclohexane dimethanol with cyclohexane dimethanol divinyl ether, polylactide diol with cyclohexane dimethanol divinyl ether.

The active polyacetal blocks are based on active alcohols which are linked together by acetal units such that on release these active alcohols cause a physiological effect ie stimulate or inhibit biological processes with the aim of improving healing, suitable examples are monobutryin, hydrocortisone, cholesterol.

The following property enhancements can be obtained through the buffering effect of calcium carbonate (I) Stabilisation of polymer during processing (II) Degradation regulator (II) Modulus improver (IV) Osteoconductive anchoring points. Rate modifying agents may be incorporated into polymers or polymer blends as hereinbefore described by, for example, polymerisation or physical blending. These agents may accelerate degradation, for example acids (e.g. fatty acids, lactic acid), anhydrides (e.g. lauric anhydride) or cyclic esters (e.g. glycolide, lactide). Alternatively the agents may slow down degradation, for example by the use of buffering agents such as bases (e.g. $CaCO_3$, $MgCO_3$).

The use of acids or bases may be used to switch the degradation mechanism from hydrolytic to predominantly enzymatic. For example use of acids will accelerate the degradation of acid sensitive components (i.e. the acetal component) whilst the addition of bases will retard the acetal degradation and thus increase the relative rate of the enzyme degradable amino acid block.

According to the present invention there is further provided a method for improving the modulus of these materials by the incorporation of inorganic (particulate or fibre) and/or polymeric (fibre or particulate) fillers. The addition of inorganic fillers will also be used as an osteogenic promoting material for increasing the binding of osteoclast and osteoblasts.

The present invention further provideds a method for improving the cell binding of these materials by the incorporation of peptide sequences such as RGD, GRGDS, REDV and GREDVY groups. Other groups can be sourced from the literature (ie Synthetic biodegradable polymer scaffolds, Chapter 5 Bioactive polymers, J West , J Hubbell, 1997, ISBN 0-8176-3919-5).

The present invention yet further provides a method for improving the strength and modulus of these materials by the incorporation of ionomeric forming groups, typical examples are polycaprolactone diols which contain an acid groups (sold under the trade names CAPA HC1200 Bx (Mn= 2000), CAPA HC 1600Bx (Mn= 600) . The acid groups can the be reacted with metal salt to form metal-acid complexes ie $-CO_2Na$, $-CO_2MgO_2C-$, $-CO_2ZnO_2C-$.

The present invention also provides artefacts formed from the segmented copolymers of the invention.Such artefacts include, but are not limited to screws, suture anchors, plates, drug delivery devices and the like.

for the artefacts of the invent may find use in orthopaedic or soft tissue applications. For example said artefacts may include injectable cements for screw augmentation, fracture fixation or improvement of fracture stability, screw/anchor augmentation, ligament fixation, osteobone reinforcement (for example for use in spine applications) or drug delivery.

Figure 5. shows an example of a polyacetal structure in which:

Strength Block = main strength component of polymer

Amino acid diester/acetal block = enzyme degradable and cell compatibility block

Polyacetal block = hydrolytic degradable block

Active/polyacetal= active release block

R_1= is an organic residue derived from an amino acid.

R_2 = is an organic residue derived from an ester or carbamate. and may be derived from an alkyl-, cycloalkyl-, substituted cycloalkyl-, aryl-, substituted aryl-, or alkenyl- alcohol, in which a least one carbon has been replaced at least one C(O)NH- or C(O)O- group

R_3 = is an organic residue derived from a cyclic ester, cyclic carbonate, hydroxyacid, or amide protected amino acid

R_4 = is an organic residue derived from an ester or carbamate and may be derived from an alkyl-, cycloalkyl-, substituted cycloalkyl-, aryl-, substituted aryl-, or alkenyl- divinyl ether, in which a least one carbon has been replaced at least one C(O)NH, $C(O)NR_5$ or C(O)O group

R_5 = is a substituent carried on the divinyl ether and may take the form of a hydrogen, aliphatic alkyl, aromatic or cyclic alkane group.

R_6 = is an organic residue derived from a biologically active alcohol. Suitable examples of biologically active alcohols are monobutyrin, cholesterol, hydrocortisone.

Polymer = is residue of a homopolymer or copolymer diol. Suitable polymeric diols are derived from degradable polyesters, polycarbonates, polyester-carbonates, polyamides, polyamide-esters, polyamide-carbonates or polyurethanes. Examples are polycaprolactone, polylactic acid (D, L or mixture), polyglycolide, polydioxanone, polydimethyl trimethylene carbonate (DMTMC). The polymer blocks suitably have one or more of the following characteristics: (a) glass transition temperature (Tg) above body temperature, (b) crystallinity, (c) hydrogen bonding properties or (d) forms stereo complexes.

Examples

1. Preparation of polyacetals containing different sized polycaprolactone blocks

The polycaprolactone diols (PCL) in the amounts shown in Table 1a were respectively placed into 125 ml Wheaton glass vials, together with the corresponding amounts p-toluene sulfonic acid monohydrate (TSA) also shown in Table 1aand 50ml of anhydrous chloroform.The vials sealed (silicon stopper/aluminium crimp cap) and and the reactants stirred using a magnetic stirrer at room temperature. Cyclohexane dimethanol divinyl ether (CHDMDVE)/anhydrous chlororm (1ml /10 ml)) solutions was prepared and these were then added in small aliquots over time to each of the vials . Neat CHDMDVE (1 ml and 4 ml) was added to the reactants using low molecular weight PCL diol (Mn= 1250 and Mn= 580 respectively) in order to reduce the volume of chloroform added to these reactions. Once the reactant mass had become viscous an additional 20 ml of anhydrous chloroform was added to reduced the solution viscosity. These solutions were passed through a Al_2O_3 / glasswool column and collected in vials containing $CaCO_3$ (2% wt/wt). The $CaCO_3$ was dispersed and the resulting solutions cast onto release paper, molecular weights of the resulting polymers were detrermined using GPC.

Molecular weight of polycaprolactone diol	PCL (g)	p-TSA (g)	Total CHDMDVE/ total addition time	Mn	Mw
Mn 10 000	10.06	0.006	*0.43 ml/ 165 min*	*48365*	*98805*
Mn 4000	9.96	0.004	*0.56 ml/ 178 min*	*36290*	*96410*
Mn 1250	10.33	0.008	*1.60 ml/195 min*	*42975*	*107450*
Mn 530	10.16	0.004	*4.5/ 248 min*	*46895*	*131200*

Table 1a. Table showing formulations and final molecular weights of Polyacetal (PCL/CHDMDVE) films.

Tensile properties

Above materials were moulded into1 mm thick flat sheets using a heated press (90C). Tensile dumbbells were cut tensile and tested on a Zwick 1435 tensile test machine (test speed of 10mm/min, gauge length =10mm).

PCL (MWT)	Ultimate tensile strength (M Pa)	Modulus (M Pa)
10 000	13.0	223
4000	8.05	300
1250	2.05	9.8
580	-- too weak	to test
PCL only (Control) (Mn= 38 000)	18.6	245

Table1b: Data shows effect of block size on final properties of polyacetal polymer.

PCL block size (Mn)	T_o(°C)	T_m(°C)	ΔH_f (J/g)	T_c(°C)	*Set in water (37 or 20C)*
10 000	60.3	67.3	94.7	20.9	Yes/ 37C
4 000	59.5	64.4	110.7	24.2	Yes/ 37C
1250	44.7	53.1	69.3	15.7	Yes/ 20C
530	23.5	40.5	41.8	3.6	no
PCL Control					
37 000	56.3	60.8	84.8	25.9	Yes/ 37C

Table 1c. Effect of block size of PCL on melting and setting temperatures of PCL based polyacetals (all polyacetals have Mn of approx. 40 000).

2. Accelerated degradation of Polyacetal (PCL (4000)/ vectromer 4060) using accelerant

Polycaprolactone diol (Mn 4000, 11.7 g) was placed into a 125 ml glass vial. p-Toluene sulfonic acid monohydrate (pTSA, 0.023g) was added to the vial,

followed by 40 ml of anhydrous chloroform. This was stirred using a magnetic stirrer at room temperature. A vectromer 4060(bis[4-(vinyloxy)butyl]adipate) (1.7g)/ chloroform (15 ml) soln was prepared. This was then added in small aliquots over time until the solution became viscous (10 ml over 1 hr) . Anhydrous chloroform (20 ml) was also added to reduce the viscosity of the solution. Sodium hydrogen carbonate soln (1 M, 2ml) was added and mixed for 15 mins. The polymer was then precipitated and air dried. The final material was dried in a vacuum oven. 3 g of the above polyacetal was dissolved in chloroform (50 ml/ anhydrous). Lauric acid (LA, 0.15g, 5 % wt/wt) was added and the solution mixed. The solvent was than removed by casting the solution onto release paper and air dried. The resulting polymer/LA blend was further dried in a vacuum oven (1 hr/ room temperature). 2g of the polymer/LA blend was placed into clean small PTFE pot, heated to 90C, moulded (5 mins), cooled (room temperature) to yield a small polymer plug (18 mm dia). An accelerated degradation experiment was carried out using this polyacetal (PCL/vectromer 4060) sample, phosphate buffer solution (50 ml) and a sealed plastic vial. The degradation experiment was carried out at 45C/ pH 7.4. The plugs were removed at each time point, wiped dry and a small piece (0.1 g) removed for GPC (chloroform/PS standards) analysis. The plugs were then placed back into the buffer soln and degraded until the following time point was reached.

Material	time/ days	Mn (X 1000)	Mw (X 1000)
Polyacetal (PCl [4K]/ Vectromer 4060)	0	46	95
	20	43	93
	41	40	96
	115	41	91
Polyacetal (PCl [4K]/ Vectromer 4060)/ 5% lauric acid	0	46	95
	10	36	78
	31	27	62
	105	26	56

Table 2. Effect of acid accelerant on PCL based polyacetal.

3. Preparation of polyacetals using PCL (Mn 4000) of different block ratios

Polycaprolactone diol (Mn 4000) and cyclohexane dimethanol(CMDM) were placed into 125 ml glass vials. p-Toluene sulfonic acid monohydrate (pTSA) was added to the vial, followed by 40 ml of anhydrous chloroform. The solutions were stirred using a magnetic stirrer at room temperature. Neat CHDMDVE (3 ml and 2 ml) was added to the respective reactions. Cyclohexane dimethanol divinyl ether (CHDMDVE) (1ml/10 ml) solutions were prepared, using anhydrous chloroform, and added in small aliquots until the solutions became viscous. 20 ml of anhydrous chloroform was then added, the resulting solution mixed and then passed through a Al_2O_3 / glasswool colum. The resulting solution was collected into separate vials containing $CaCO_3$, mechanical mixed to disperse the $CaCO_3$ and cast onto release paper.

PCL (g)	CHDM (g)	p-TSA (g)	Total CHDMDVE (ml)/ Total addition time	Mn	Mw
5.00	3.01	0.005	4.3 ml/ 165 min	48770	115900
7.51	1.54	0.004	2.8 ml/ 167 min	47380	127700

Table 3a: Table showing formulations and final molecular weights of Polyacetal (PCL/CHDM/CHDMDVE).

Mechanical properties

Above materials were moulded into1 mm thick flat sheets using a heated press (90C). Tensile dumbbells were cut and tested on a Zwick 1435 tensile test machine (test speed of 10mm/min, gauge length =10mm).

Polymer	Ultimate tensile strength (M Pa)	Modulus (M Pa)	Mode of failure
PCL only (Mn= 38 000)	18.6	245	Some breaking below Yield stress, after long yield (Yield then quoted)
Polyacetal (PCL (4000)/ CHDMDVE)	8.05	300	Snap @ max stress
Polyacetal (PCL (4000)/ CHDM)/ CHDMDVE) (50 % PCL)	4.65	24	Snap @ Max stress (after long pull-out)

Table3b: Data shows effect of block size on final properties of Polyacetal (PCL/CHDM/CHDMDVE) polymer.

Sample No.	T_o(°C)	T_m(°C)	ΔH_f (J/g)	T_c(°C)
Polyacetal (PCL[4000]]CHDM/CHDMDVE) (50 % PCL)	39.6	46.4	30.1	-
polyacetal (PCL [4000] /CHDM/ CHDMDVE) (75 % PCL)	46.9	54	37.75	-7.9
Polyacetal blend [polyacetal (PCL [4000] /CHDMDVE) blended with Polyacetal (CHDM/CHDMDVE) (50:50)]	36.2	46.4	46.7	14

Table 3c: Effect of Polyacetal (PCL/CHDM/CHDMDVE).composition on melting and setting properties (all polyacetals have Mn of approx. 40 000).

Thermoplastic elastomer

Polyacetal (PCL[4 000)]CHDM/CHDMDVE) (50 % PCL) was noted to cold draw to an aligned thermoplastic elastomeric, which stretches (on application of force) and recovers initial dimensions on relaxation of force.

4. Preparation of polyacetal using PCL (Mn 4000) and monobutyrin

PCL diol (Mn 4000) and cyclohexane dimethanol were dried at 60°C in a vacuum oven. The monobutyrin was dried at room temperature in a vacuum oven. Catalyst (p-TSA) was added to the PCL / CHDM mixtures and

monobutyrin was then added. 50 ml of anhydrous chloroform was added and the mixture stirred at room temperature. The reagents were polymerised by the addition of CHDMDVE/ anhydrous chloroform (1.0 ml/10 ml) solution , as shown in table 4a, until the polymerisations solutions became viscous. The mixture was diluted with 20 ml of anhydrous chloroform and the solution passed through an Al_2O_3/glasswool column. All solutions were collected in separate vials containing $CaCO_3$ (2% wt/wt), mechanically mixed to disperse the $CaCO_3$ and cast on a release paper to yield the following two Polyacetal (PCL/CHDM/Monobutyrin/CHDMDVE).

PCL (g)	CHDM (g)	Mono butyrin (g)	p-TSA (g)	Total CHDMDVE (ml)/ Total time	Mn	Mw	Monobutyrin incorporation (g)
5.08	2.09	0.946	0.003	4.5 ml/ 117 min	48400	140900	3.5%
5.02	0.9	0.4	0.0056	2.5/ 60 min	38980	217200	2.4%

Table 4a: Table showing formulations and final molecular weights of Polyacetal (PCL/CHDM/Monobutyrin/CHDMDVE).

Composition	Ultimate tensile strength (MPa)	Modulus (MPa)	Mode of failure
Polyacetal (PCL [4000]/CHDMDVE)	8.05	300	Snap @ max stress
Polyacetal (PCL [4000]/ CHDM/ CHDMDVE) (50% content =PCL)	4.65	24	Snap @ Max stress (after long pull-out)
Polyacetal (PCL [4000]/ CHDM/ CHDMDVE) acetal blocks + 3.5% monobutyrin (50% content =PCL)	4.20	20.6	Snap @ max stress
Polyacetal (PCL [4000]/ CHDM/ CHDMDVE) acetal blocks + 2.4% monobutyrin (75% content =PCL)	5.67	33.4	Slow breaking @ max stress after lower maxima yield & long pull-out

Table 4b: Table shows the effect of incorporation of monobutyrin on tensile properties of PCL based Polyacetal.

5. Preparation of polyacetal(PCL[CHDM/CHDMDVE) using bulk polymerisation methodologies.

Preparation of catalyst.

5.00 g of PCL diol (Mn 4 000)and 0.0036 g of p-toluene sulphonic acid monohydrate (pTSA) were weighed into a 60 ml glass jar then heated in an oven at 100°C. Once the PCL had melted the contents were mixed thoroughly with a spatula to produce a solution then allowed to cool. The mixture was re-warmed in an oven at 65°C to produce a clear liquid before use.

Polyacetal (PCL[4000)]CHDM/CHDMDVE) (72 % PCL)

7.5g of PCL diol , 1.06g CHDM and 1.81g of CHDMDVE were weighed into a 60ml glass jar then heated in an oven at 100°C. Once the PCL had melted the contents were mixed with a spatula to produce a homogenous mixture. The jar was then transferred to a 65°C oven and once it had equilibrated at this temperature, 0.30 g of the catalyst in PCL was added and the contents mixed thoroughly with a magnetic stirrer. The jar was then sealed and returned to the 65°C oven. Samples were removed from the jar for molecular weight analysis after 4 days of reaction, the results are shown in table 5a.

Polyacetal (CHDM/CHDMDVE)

8.46g CHDM and 11.53g of CHDMDVE were weighed into a 60ml glass jar then heated in an oven at 100°C. Once CHDM had melted the contents were mixed with a spatula to produce a homogenous mixture. The jar was then transferred to a 65°C oven and once it had equilibrated at this temperature, 0.47 g of the catalyst in PCLdiol was added. The contents were mixed thoroughly with a spatula and the jar sealed and returned to the 65°C oven. The CHDM and CHDMDVE were found to be immiscible, and were initially removed from the oven, remixed and replaced in the oven several times before being removed and allowed to cool overnight as no increase in viscosity had been observed. The jar was then placed in water bath, heated at up to 65°C and stirred with a magnetic stirrer. After half a day of mixing, the

materials had reacted to form a clear viscous liquid. The jar was then removed from the water bath and placed back in the 65°C oven. Molecular weight analysis of the material was carried out after after 6 of reaction, the results are shown in table 5a.

Sample	Mw	Mn
28% polyacetal, 4 days reaction	54475	25900
100% polyacetal, 6 days reaction	25760	9622

Table 5a. Molecular weight distribution of reaction samples

6 Polymer blend

Polyacetal (PCL/CHDMDVE)/ Polyacetal (CHDMDVE/CHDM) was prepared by dissolving 2g of Polyacetal (PCL/CHDMDVE) and Polyacetal (CHDMDVE/CHDM) in chloroform (50 ml). The resulting was cast on release paper. Final molecular weight of blend was Mn=17825, Mw=116800.

7 Applications of In situ setting properties of PCL based polyacetals

7a Novel in situ forming anchor

Four anchor systems were investigated using a commercial polyethylene terephthalate (PET) Ashway # 2 suture. The liquid anchor materials chosen were pure ε-polycaprolactone (PCL), mw = 37 000, polyacetal (PCL(Mn = 4 000)/CHDMDVE), and polyacetal (PCL(Mn = 4 000)/CHDMDVE)/ PCL(Mn= 4000) blend. For comparative purposes, a solid OBL RC5 anchor was also selected for study.

Two (Ø2 mm x 10 mm) holes, 7 mm apart, were drilled into a block of 20 pcf Sawbone (40 x 20 x 20 mm). Each hole was filled with a polymer preheated to 70°C, and a length of suture was placed into the two holes using a hand held tool. The height of the loop formed was fixed at 3.5 mm, which is thought to be wide enough to allow adequate fixation of the supra-spinatus tendon to the

bone, and subsequent healing of the rotator cuff injury. For the solid anchor systems, two (Ø5 mm x 10 mm) holes were drilled and metal anchors were inserted into these holes using anchor drivers counter sunk to between 0.5 and 1 mm below the surface. Mechanical testing was carried out using an 8511 servo-hydraulic tensile tester fitted with an environmental chamber filled with water heated to 37°C. Each Sawbone block tested was clamped in a g-clamp, and the suture loop, emerging from the block, was attached to the supporting clips which were fed through the holes of the T-piece. This was then held in 30 kN capacity wedge action grips attached to a 1 kN capacity static load cell which was in turn mounted on the actuator of the machine. Pull-out testing was carried out perpendicular to the surface of the Sawbone block at a speed of 32 mm/s until failure occurred, which is either by rupture or by pull-out of the suture device. The load-to failure data were collected on a personal computer and the results were assessed with a force-time diagram. For each anchor system tested, a mean pull-out force was determined from five independent samples.

Material for anchor augmentation	Failure force (N)	Variance
PCL	98.5	17.3
1L-2 Polyacetal (PCL(Mn = 4 000)/CHDMDVE)/ PCL(Mn= 4000) blend	88	12
1L-2 polyacetal (PCL(Mn = 4 000)/CHDMDVE)/ PCL(Mn= 4000) blend	90.2	20
Suture	143	0.14
IL-2 RC5	132	7.7

Table 7a. Failure force for in situ formed anchors produced using polyacetals.

8 Synthesis of PLA based Polyacetal

8.1 Synthesis of Poly(L) lactide diol

Lactide (49.5g) was placed into 125 ml Wheaton vial and the vial sealed with a silicon stopper and aluminium crimp cap. 1 ml of a tin (ii) dilaurate (0.1g)/diethylene glycol (5g) suspension was then added. The vial was placed into an oven (135C) and heated until all the monomer had melted. The vial

was manually agitated during this period. The vial was then heated (135 C) for 69.5 hr to yield a white crystalline solid. The temperature was increased to 165C and the resulting PLA melt heated for 6 hr. All samples were removed from the oven and cooled to room temperature to yield a white solid. The solid was dissolved in chloroform (80 ml) and precipitated into methanol (2 X 800 ml). The resulting polymer was collected and dried (air and vacuum oven (5hr / 70C). The polymer was dried overnight at room temperature/under vacuum (1mm Hg). The resulting polymer had an Mn = 7400/ Mw = 10804).

8.2 Synthesis of Polyacetal (PLA/CHDM/CHDMDVE)

The following is a general procedure used in the synthesis of polyacetal (PLA/CHDM/CHDMDVE) (50% PLA). The same method, with adjusted reagent ratios, was also used to produce other polyacetals (PLA/CHDM/CHDMDVE) materials with PLA contents between 50-90%, table 8a below.

Poly-l-lactic acid diol (6g, Mn = 7400/ Mw = 10804), CHDM (2.5g) was placed into a 125 ml glass vial. p-Toluene sulfonic acid monohydrate (3.3 mg) was added to the vial and the contents dried in a vacuum oven (60C/ 4 hr). The vial was then sealed (silicon stopper/ aluminium crimp lid) and 50 ml of anhydrous chloroform was added. This was stirred using a magnetic stirrer at room temperature. The PLA diol was polymerised with (cis/trans) cyclohexane dimethanol divinyl ether (CHDMDVE), 3.3ml of neat CHDMDVE and 2 ml dilute CHDMDVE/anhydrous chloroform(1ml/ 10 ml) solution. The reaction was noted be very viscous. An additional 20 ml of chloroform was added to reduce the solution viscosity. This solution was passed through an Al_2O_3 / glasswool column and collected into a vial containing $CaCO_3$. The collected solution was mixed using mechanical rollers and cast onto release sheets, properties:- Mn = 19 800 , Mw = 47 600, Tg= -3.2C & 42C, Tm= 143.2C.

Tensile test samples were moulded using these Polyacetals (PLA/CHDM/CHDMDVE) polymers and their respective tensile properties determined.

PLA content (wt%)	Acetal content (Wt %)	Filler Type/Level	Mn (X1000)	Mw (X 1000)	U. Tensile Strength (M Pa)	Modulus (M Pa)
50	50	$CaCO_3$ / 2%	18	75	12	300
60	40	$CaCO_3$ / 4%	37	85	16.1	177
70	30	$CaCO_3$ / 4%	31.5	68	20.6	260
87	13	$CaCO_3$ / 4%	27	61	7	664

Table 8a: Table shows the effect of PLA block content on tensile properties of the Polyacetal(PLA/CHDM/CHDMDVE).

9 Degradation of Polyacetal(PLA/CHDM/CHDMDVE)

Polyacetal(PLA/CHDM/CHDMDVE) was produced using the following procedure Poly-l-lactic acid diol (4.5g, Mn= 5200/Mw= 10800)), CHDM (2.1g) was placed into a 125 ml glass vial. p-Toluene sulfonic acid monohydrate (12mg) was added to the vial and the contents dried in a vacuum oven (100 C/4 hr). The vial was then sealed (silicon stopper/aluminium crimp lid) and anhydrous chloroform (40 ml) added. This was stirred using a magnetic stirrer at room temperature. The PLA diol was polymerised with (cis/trans) cyclohexane dimethanol divinyl ether (CHDMDVE). A CHDMDVE/anhydrous chloroform solution(2.55g/ 10 ml) was prepared and aliquots added to the stirred solution over a 2 hr period. A further CHDMDVE/Chloroform (2g/10 ml) solution was prepared. 9 ml of this solution was added over 2.5hr period. The reaction became very viscous, an additional 20 ml of chloroform was added to the mixture to reduce the viscosity. The polymer was purified by passing the solution through an Al_2O_3 / glasswool column and precipitated into methanol. The final polymer was

collected and dried (air dried and vacuum .oven (60C/ 4hr)). Molecular weight of polymer Mn= 35 500/Mw= 126 000. Polymer rods (approx. 6.0 mm diameter) were produced by packing a PTFE block, containing a 6.2 mm hole with polymer. This was heated at 170 C until the polymer had become molten. The molten polymer was compressed and cooled to form a soft rod which crystallised on cooling. Small plugs (approx. 10 mm in length) were cut and degraded in both acid (pH 3) and buffer solution (pH 7.4), figure 6. The degradation data is given in table 9a below.

PH of solution	Total deg Time days	Weight (g)	Wt Change	% Wt loss (g)	Diameter / mm	Diameter change /mm	% Diameter reduction
3	0.0	0.2953	-	0	6.07	-	0
	0.9	0.2950	-0.0003	0.11	6.02	-0.05	0.82
	3.8	0.2669	-0.0284	9.6	5.89	-0.18	2.96
	4.8	0.2484	-0.0469	15.9	5.82	-0.25	4.1
	6.2	0.2265	-0.0688	23.3	5.72	-0.35	5.8
	8.2	0.2084	-0.087	29.4	5.61	-0.46	7.6
	11.1	0.1694	-0.1259	42	5.36	-0.71	11.7
	13.9	0.1471	-0.1482	50.2	5.27	-0.8	13.1
7.4	0.0	0.2657	0	0	6.08	0	0
	0.9	0.2652	-0.0005	0.19	5.95	-0.13	2.1
	3.8	0.2518	-0.0139	5.2	5.94	-0.14	2.3
	4.8	0.2433	-0.0224	8.4	5.87	-0.21	3.4
	6.2	0.2327	-0.033	12.4	5.83	-0.25	4.1
	8.2	0.2236	-0.0421	15.8	5.76	-0.32	5.3
	11.1	0.2033	-0.0624	23.5	5.65	-0.43	7.1
	13.9	0.1882	-0.0775	29.2	5.58	-0.50	8.2
	19.8	0.1710	-0.0947	35.6	5.43	-0.65	8.9
	23.9	0.1644	-0.1013	38.1	5.38	-0.7	11.5
	27.1	0.1595	-0.1062	39.9	5.28	-0.80	13.1
	31.1	0.1552	-0.1105	41.5	5.22	-0.86	14.1
	33.4	0.1518	-0.1139	42.8	5.19	-0.89	14.6
	39.4	0.1427	-0.123	46.3	5.12	-0.96	15.8
	58.3	0.1299	-0.1358	51.1	4.99	-1.09	17.9
	101.3	0.1040	-0.1617	60.8	-	-	-

Table 9a: Data shows change in weight and diameter of degrading polyacetal (PLA/CHDM/CHDMDVE) with time and pH.

10 Effect of buffering agent on thermal stability of polyacetal(PLA/CHDM/CHDMDVE)

Polyacetal (PLA/CHDM/CHDMDVE)/ $CaCO_3$ blends were produced by solution blending (PLA/CHDM/CHDMDVE) (3.5g) with $CaCO_3$ powder(3.5g) in chloroform (20 ml). The resulting solution was cast to form films and dried (air dried overnight then vacuum oven 80 C). Polymer rods (approx. 9.3 mm diameter) were produced by packing a PTFE block, containing a 9.3 mm hole, with polymer/$CaCO_3$. The mould/polymer was heated to 185C until the polymer had become molten. The molten polymer was then compressed and cooled. A opaque white rod was formed on cooling.

Material	Mn	Mw
Polyacetal (PLA/CHDM/CHDMDVE) (control)	13710	28350
Polyacetal (PLA/CHDM/CHDMDVE)/ Heat 185C	6980.5	15155
Polyacetal (PLA/CHDM/CHDMDVE)/ $CaCO_3$/ Heat 185C	9149	21685

Table 10a: Data shows the effect of temperature on the molecular weight of stabilised and unstabilised polyacetal (PLA/CHDM/CHDMDVE).

11 Effect of $CaCO_3$(buffer) on degradation of Polyacetal (PLA/CHDM/CHDMDVE)

Polyacetal (PLA/CHDM/CHDMDVE)/$CaCO_3$ rod was cut to give a plug (9.3 mm diameter X 7.55 mm length). The sample was placed into a sealed pot and degraded 37C/pH 7.4 in phosphate buffer solution.

Sample Polyacetal (PLA/CHDM/CHDMDVE)	Total degradation Time days	Weight (g)	% Wt change (g)	Diameter / mm	% Diameter change
Contains 50% (wt/wt) $CaCO_3$ buffered					
	0.0	0.7407	0	9.31	0
	3.7	0.7395	- 0.16	9.32	+0.11
	5.6	0.7386	- 0.28	9.30	-0.11
	11.3	0.7371	- 0.48	9.285	-0.27
	16.3	0.7332	-1.01	9.26	-0.54
	35.1	0.7261	-1.96	9.22	-0.97
	80.1	0.7149	-3.48	9.11	-2.14
	230.1	0.6948	- 6.9	9.05	-2.8
No $CaCO_3$					
	0.0	0.2657	0	6.08	0
	0.9	0.2652	- 0.19	5.95	-2.1
	3.8	0.2518	- 5.2	5.94	-2.3
	4.8	0.2433	- 8.4	5.87	-3.4
	6.2	0.2327	-12.4	5.83	-4.1
	8.2	0.2236	-15.8	5.76	-5.3
	11.1	0.2033	-23.5	5.65	-7.1
	13.9	0.1882	-29.2	5.58	-8.2
	19.8	0.1710	- 35.6	5.43	-8.9
	23.9	0.1644	- 38.1	5.38	-11.5
	27.1	0.1595	- 39.9	5.28	-13.1
	31.1	0.1552	- 41.5	5.22	-14.1
	33.4	0.1518	- 42.8	5.19	-14.6
	39.4	0.1427	- 46.3	5.12	-15.8
	58.3	0.1299	- 51.1	4.99	-17.9
	101.3	0.1040	- 60.8	-	-

Table 11a: Data shows the effect of $CaCO_3$ on weight and diameter of degrading polyacetal (PLA/CHDM/CHDMDVE) with time .

12 Use of inorganic filler to enhance the modulus of PLA based Polyacetals

Polyacetal (PLA/CHDM/CHDMDVE)/ /$CaCO_3$ containing 50% Hydroxyapitite (HA) was produced by solution blending Polyacetal (PLA/CHDM/CHDMDVE)/(50% Wt PLA)/ $CaCO_3$ with HA particles (Ceramed). The resulting solution was cast and dried. Tensile samples were produced by compression moulded the blend using the Fontijne heated hydraulic press to produce a 15cm round sheets. Tensile samples were produced by cutting dumbbells using the 5mm short dumbbell cutter and an Atom SE8 hydraulic clicker press.

PLA content (wt%)	Acetal content (Wt %)	Filler Type/Level	Mn	Mw	U. Tensile Strength (M Pa)	Modulus (M Pa)
50	50	$CaCO_3$ (2%)	18000	75000	12	300
50	50	$CaCO_3$ (2%) HA (50%)	14000	65000	12.6	900

Table 12a: Data shows the effect of filler level on modulus of polyacetal (PLA/CHDM/CHDMDVE) with time.

13 Synthesis of Polyacetal (PLA/CHDM/amino acid diester/CHDMDVE)

The reaction path following the scheme below:-

Step 1 $2NH_2\text{-}R_1\text{-}CO_2H + HO\text{-}R_2\text{-}OH \rightarrow NH_2\text{-}R_1\text{-}CO2\text{-}R_2\text{-}O2C\text{-}R_1\text{-}NH_2 + 2H_2O$

Step 2 $NH_2\text{-}R_1\text{-}CO2\text{-}R_2\text{-}02C\text{-}R_1\text{-}NH_2 + R_3C{=}O \rightarrow$

$HO\text{-}R_3\text{-}CONH\text{-}R_1\text{-}C02\text{-}R_2\text{-}02C\text{-}R_1\text{-}NHCO\text{-}R_3\text{-}OH$

Step 3 $HO\text{-}R_3\text{-}CONH\text{-}R_1\text{-}CO2\text{-}R_2\text{-}O2C\text{-}R_1\text{-}NHCO\text{-}R_3\text{-}OH + HO\text{-}R_2\text{-}OH +$

$CH_2{=}C(R_5)\text{-}O\text{-}R_4\text{-}O\text{-}C(R_5){=}CH_2 +$ HO-POLYMER–OH

$\rightarrow \{[O\text{-POLYMER-}O\text{-}CH(R_5)\text{-}OR_4\text{-}OCH(R_5)\text{-}]_m\text{-}[O\text{-}R_2\text{-}O\text{-}CH(R_5)\text{-}OR_4\text{-}OCH(R_5)\text{-}]_P\text{-}[O\text{-}R_3\text{-}CONH\text{-}R_1\text{-}CO_2\text{-}R_2\text{-}O_2C\text{-}R_1\text{-}NHCO\text{-}R_3\text{-}O\text{-}CH(R_5)\text{-}OR_4\text{-}OCH(R_5)\text{-}]_n\text{-}\}_r$

m = 1-100, n = 0-100, p = 0-100, r = 1-100

Step 1: Diamino ester

L-Phenylalanine (16.5g, 0.1 moles) was reacted with cyclohexane dimethanol (7.2g, 0.05 moles) and p-toluene sulfonic acid monohydrate (20g, 0.105moles). These reagents were heated in 130 ml toluene under reflux using a Dean Stark head in order to collect the water. A volume of 2.6 ml of water was collected. The toluene solvent was removed on a rotary evaporator to leave a crude white powdery product. The white powder was purified by washing with absolute alcohol (3X 80 ml) and drying the resulting product to constant weight in a vacuum oven. The product was suspended in 200 ml of deionised water (80C) and neutralised with potassium carbonate (10 g). Gas(

CO2) was evolved resulting in the formation of an oil/water emulsion. On cooling to room temp this yielded a light brown solid. The solid was collected, dissolved in chloroform, dried with magnesium sulphate, filtered and the solution reduced on a rotor evaporator to yield a brown-cream solid. Structure of diamino ester was confirmed using ^{1}H-NMR and the FT-IR.

Step 2: Diamino ester/caprolactone adduct

Diphenylalanine ester (2.5g) and caprolactone (2.5 g) were placed into a Wheaton vial (10 ml). The vial was sealed (silicon stopper & aluminium crimp cap) and placed in an extracted oven at 105C (2hr) then 150C (5 hr), the sample was manually agitated during this period. It was noted that the diester melted quickly and became soluble in the caprolactone to yield a yellow product. The sample was reacted for further 14 hrs, removed and cooled to yield a viscous brown liquid. Structure of diamino ester confirmed using ^{1}H-NMR and the FT-IR.

Degradation of diphenylalanineester/caprolactone adduct using Chymotyrpsin

Approximately 1.0 g of diphenylalanine ester/caprolactone adduct was placed into 2 separate polypropylene containers (25 mm X 5.5 mm). These were placed into 2 polycarbonate jars(25 ml). Materials were then degraded by exposing the materials to either (I) chymotrypsin solution or (II) Tris buffer solution. These solutions were prepared by:-

(a) Producing a stock enzyme solution containing 0.5g of Chymotyrpsin in 3.366 ml of 1.0 mM HCL. This was used to make a 25 ml enzyme solution having an activity of 500 units/ml by adding Tris Buffer Solution (22.67 ml), 2M $CaCl_2$ Solution (0.675 ml) and stock enzyme solution (1.65 ml) into a polycarbonate pot. 10 ml of this solution was transferred into a 25 ml polycarbonate pot containing a diphenylalanine ester/caprolactone adduct sample.

(b) The buffer (control) solution was prepared using a similar method. This was then made by adding Tris buffer Solution (22.67 ml), 2M $CaCl_2$ Solution (0.675 ml) and dilute HCl solution (1.65 ml) into a sealed polycarbonate pot.

10 ml of this solution was transferred into a 25 ml polycarbonate pot containing a diphenylalanineester/caprolactone adduct sample.

All samples were incubated at 37 C with mechanical agitation. Samples were removed from there respective solutions, air dried (2 days) and weighted. These samples were then further degraded in the respective solutions. The degradation solutions were also changed ever 3 days to ensure a high activity of the enzyme.

Degradation media	Time	Mass loss (%)
Chymotrypsin (500 units), tris buffer/ 37C		
	0	0
	48	9.1
	145	26.9
	193	36.5
	262	51.4
	310	58.6
	363	65.7
	450	74.2
Tris buffer/ 37C		
	0	0
	48	-0.86
	145	1.81
	193	3.73
	262	5.8
	310	7.3
	363	8.9
	450	9.8

Table 13a: Enzymatic and hydrolytic degradation of diamino ester/caprolactone block containing 5 units of caprolactone

Step 3: PLA based Polyacetal containing diamino ester/caprolactone adduct

Polyacetal(PLA/CHDM/CHDMDVE/phenylalanine ester-caprolactone adduct) was produced using the following procedure: Poly-l-lactic acid diol (4g, Mn= 5200/Mw= 10800) and diphenylalanine ester/caprolactone (3.0g) adducts were placed into a 125 ml glass vial. p-Toluene sulfonic acid monohydrate(16

mg) was added to the vial and the contents dried in a vacuum oven (100 C/4 hr). The vial was then stoppered (silicon stopper/aluminium crimp lid) and 30 ml of anhydrous chloroform was added. This was stirred using a magnetic stirrer at room temperature. The PLA diol was polymerised with (cis/trans) cyclohexane dimethanol divinyl ether (CHDMDVE). A CHDMDVE/anhydrous chloroform solution (2g/ 10ml) was prepared and added in small aliquots. The resulting solution was noted to become cloudy. The solution was then filtered, via a syringe fitted with a 0.45um nylon filter, into a separated sealed Wheaton vial (125ml) containing CHDM (1.0g), magnetic stirrer and p-TSA (10 mg). This formed a clear straw yellow solution. 9 ml of a CHDMDVE/chloroform solution (1.23g/10 ml chloroform) was added over a 2 hr period. The resulting viscous solution was purified by passing the solution through an Al_2O_3 / glasswool column, precipitating into methanol and dried to remove residual solvent. The polymer structure was confirmed using FTIR and NMR. Polymer rods (approx. 6.0 mm diameter) were produced by packing a PTFE block, containing a 6.2 mm hole, with polymer. The resulting mould was heated at 180 for 10 mins until the polymer had become molten. The molten polymer was then compressed and cooled to form a soft rod which crystallised on cooling.

Polymer	Mn	Mw
Initial polymer	42560	111150
Heated to form plug	30555	78300

Table 13b: Data shows the effect of heat on polyacetal (PLA/CHDM/CHDMDVE/phenylalanine ester-caprolactone) during the moulding process.

14. Degradation PLA based Polyacetal containing diamino ester/caprolactone adduct

Polyacetal (PLA/CHDM/CHDMDVE/ phenylalanine ester-caprolactone adduct) were produced using the above method. Polymer plugs were cut from the polyacetal rod using a diamond saw. The enzymatic degradation of these

materials was then evaluated by degrading the polymers plugs at 37C/ pH7.8/ in 10ml of enzymatic or buffer solutions. The protocols for the preparation of the enzyme and buffer solution are given in example 13.

Sample Polyacetal(PLA/CHDM/CHDMDVE/ phenylalanine ester-caprolactone adduct)	**Total deg Time days**	**Weight (g)**	**% Wt change (g)**	**Diameter/ mm**	**% Diameter change**
Buffered solution	0	0.1392	0	5.86	0
	2	0.1396	+0.26	5.86	0
	9	0.1379	-0.95	5.85	-0.2
	19.8	0.128	-7.2	5.84	-0.34
	23.8	0.1261	-9.4	5.84	-0.34
Enzyme solution	0	0.1750	0	5.94	0
	1.16	0.1755	+0.27	5.95	+0.16
	9	0.1741	-0.52	5.91	-0.50
	19.8	0.1409	-19.5	5.76	-3.03
	23.8	0.1280	-26.8	5.59	-5.9

Table 14a: Enzymatic and hydrolytic degradation of Polyacetal (PLA/CHDM/CHDMDVE/ phenylalanine ester-caprolactone adduct)

15. Polyacetal(PLA/CHDM/CHDMDVE/Tryptophan diester-CL adduct)/ $CaCO_3$ blend

Polyacetal(PLA/CHDM/CHDMDVE/Tryptophan diester-CL adduct) was prepared using the above methodology. Polymer structure was confirmed using FTIR and NMR and the molecular weight via GPC (Mn = 23 900 and Mw= 152 600). 3g of Polyacetal(PLA/CHDM/CHDMDVE/Tryptophan diester-CL adduct) placed in glass vial containing $CaCO_3$ (3g) powder. Dichloromethane (10 ml) was added and the solution agitated until all the polymer had dissolved. The solution was cast and dried to remove residual solvent. A rod was moulded by packing the polymer blend into a PTFE mould (9.mm diameter hole), heated (160C) and cooled to yield a polymer rod.

Polymer	Mn	Mw
Initial polymer	23 900	152 600
Heated to form plug (180C/10 min)	17 000	131 000
Polymer/$CaCO_3$ heated to form plug (180C/ 10 min)	17 000	205 000

Table 15a: Data shows the effect of heat on polyacetal (PLA/CHDM/CHDMDVE/Tryptophan ester-caprolactone adduct) during the moulding process.

16. Cell adhesion

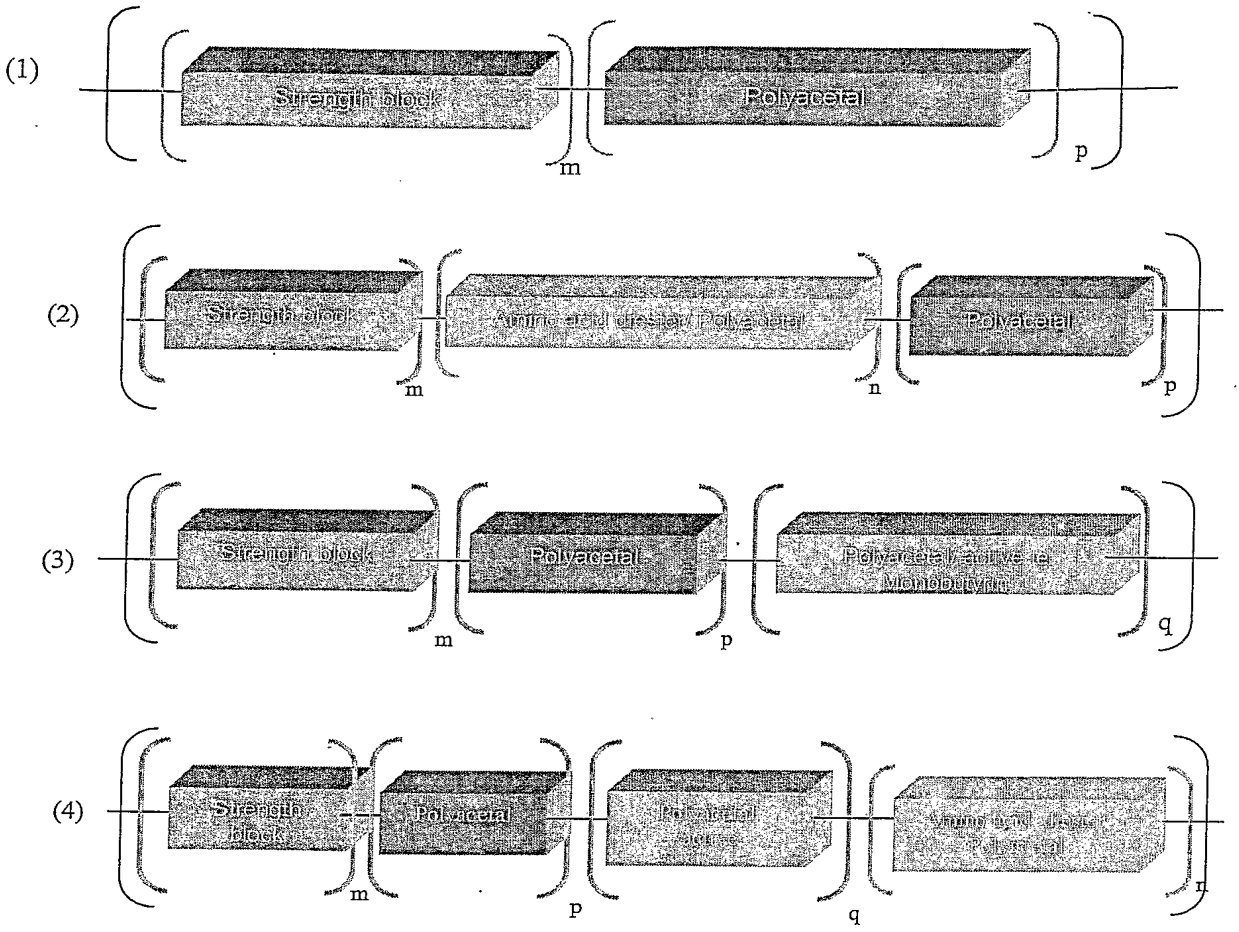
Cell binding was found to be dependent upon the chemical composition of the Polyacetal. Human peripheral blood derived osteoclasts were differentiated *in situ* on discs of polyacetal test materials. Polyacetal-(tryptophan diester/PLA), polyacetal-(tryptophan diester/PLA)/ $CaCO_3$, polyacetal-(PLA/CHDM/ CHDMVE), polyacetal-(PLA/CHDM/CHDMVE)/$CaCO_3$ and control materials were tested over the 4 week culture period during which the osteoclast progenitor cells differentiated into mature osteoclasts, Figure 7. After 6 and 19 days in culture, cells were observed attached to the control materials and polyacetal-(tryptophan diester/PLA)/$CaCO_3$. Further cells were attached to the polyacetal-(tryptophan diester/PLA). There were also no cells attached to the polyacetal-(PLA/CHDM/CHDMVE) or polyacetal-(PLA/CHDM/CHDMVE)/ $CaCO_3$ after 12 days in culture. These effects do not appear to be caused by the materials having cytotoxicity issues.

Bulk material cytotoxicity testing of the materials, using preosteoblastic MC3T3-E1, cultured around discs of the materials indicated that the materials did not exert a gross cytotoxic effect on cells, figure 8. The lack of cells attached to the polyacetal-(tryptophan diester/PLA), polyacetal-(PLA/CHDM/CHDMVE) and polyacetal-(PLA/CHDM/CHDMVE)/$CaCO_3$ can be related to their degradation rate *in vitro* and suggests that the cells were lost due to erosion of the discs surface. Where as cells were still present on the polyacetal-(tryptophan diester/PLA)/$CaCO_3$ discs which coincided with this material having the lowest degradation rate *in vitro*.

Cell viability experiments were also carried out using a WST method. Polyacetal samples were degraded in acid (pH 3), 37C for 2 wk. The solution were then neutralised with Na_2C0_3. Various concentrations of degradation solutions were prepared by using a serial dilution method, using culture medium. MC3T3-E1 (osteoblast-like) were then cultured for 24 h with test solutions. Cell viability was assayed. Control solutions were produced from (I)LDPE conditioned medium and (II)PVC/Tin conditioned medium. The cytotoxicity of both glycolic and lactic acid were measured as controls. The highest tolerated concentration of glycolic acid showing >90% cell viability was 0.1mg/ml whilst the highest tolerated concentration of lactic acid showing >90% cell viability 0.5mg/ml.

Polyacetal(PLA/CHDM/CHDMVE/Phenylalanine diester-caprolactone)						
Concentration (mg/ml)	0.5015	0.2507	0.1253	0.0627	0.0313	0.0157
Cell viability (Mean cell viability expressed as % of medium only control)	106	103	89.5	90.3	97.1	97.6
Polyacetal(PLA/CHDM/CHDMVE)						
Concentration (mg/ml)	3.153	1.576	0.788	0.394	0.197	0.098
Cell viability (Mean cell viability expressed as % of medium only control)	0	87.8	107.4	100.5	97.1	97.6

Table 16a : WST Cell viability experiment data showing cell viability with degradation products generated from the accelerated degradation of polyacetal(PLA/CHDM/CHDMVE/Phenylalanine diester-caprolactone) and Polyacetal(PLA/CHDM/CHDMVE)



Figures 1 to 4: Polyacetal structure

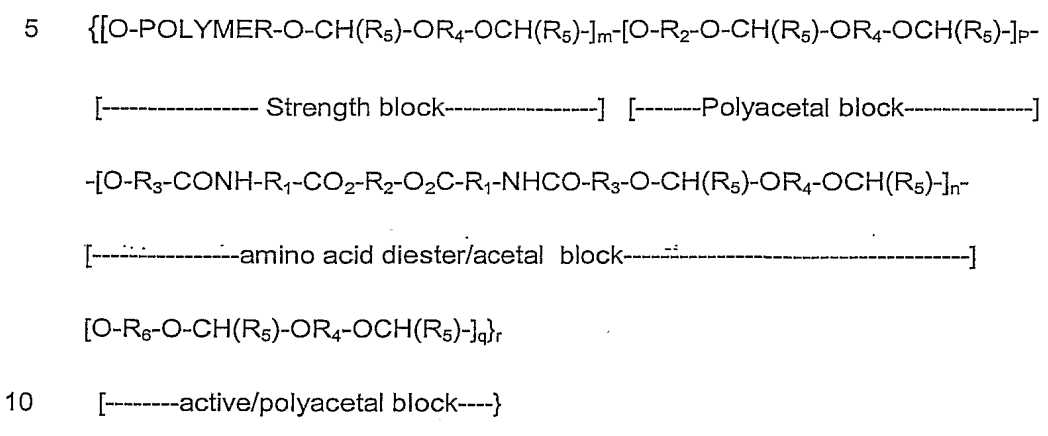
Strength Block = main strength component of polymer

Amino acid diester/acetal block = enzyme degradable and cell compatibility

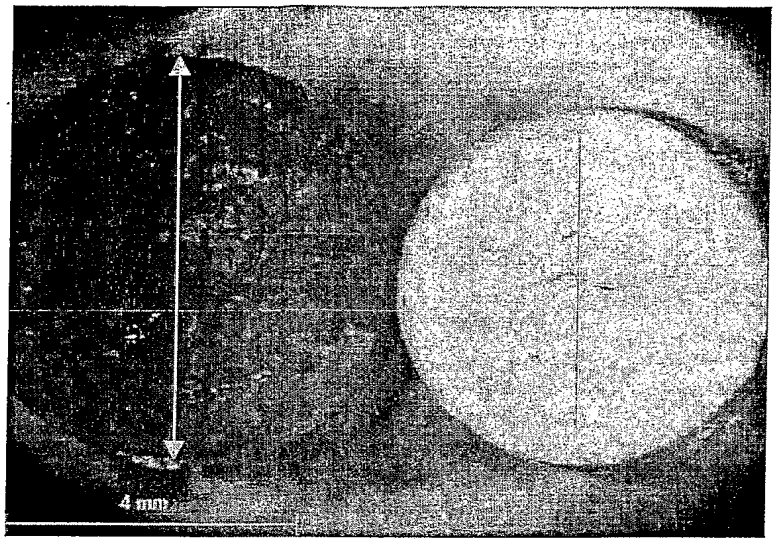
Polyacetal block = hydrolytic degradable block

Active/polyacetal= active release

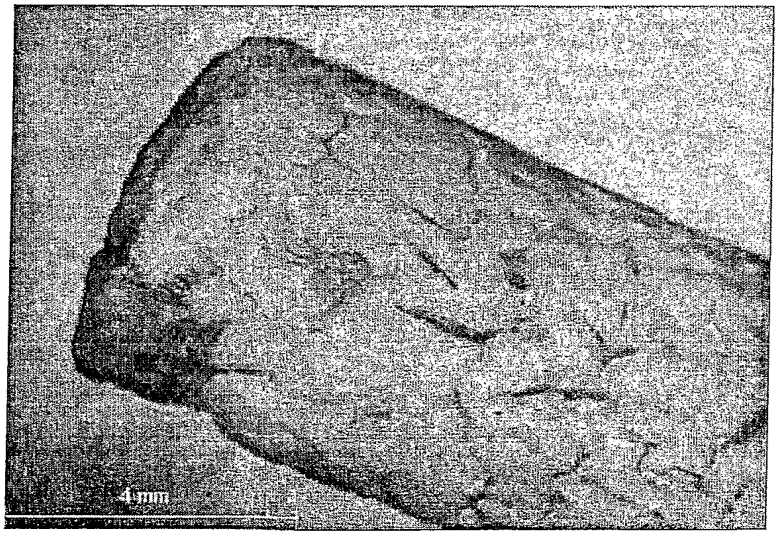
Figure 5. Polyacetal Structure



m = 1-100, n = 0-100, p = 0-100, q = 0 -100, r = 1-100



(6a)



(6b)

Figure 6: Polyacetal (PLA/CHDM/CHDMDVE) degraded in pH 7.4 phosphate buffer solution.

(6a) Reduction in diameter of initial polyacetal after approximately 9 days degradation in buffer

(6b) Effect of degradation on surface of polyacetal.

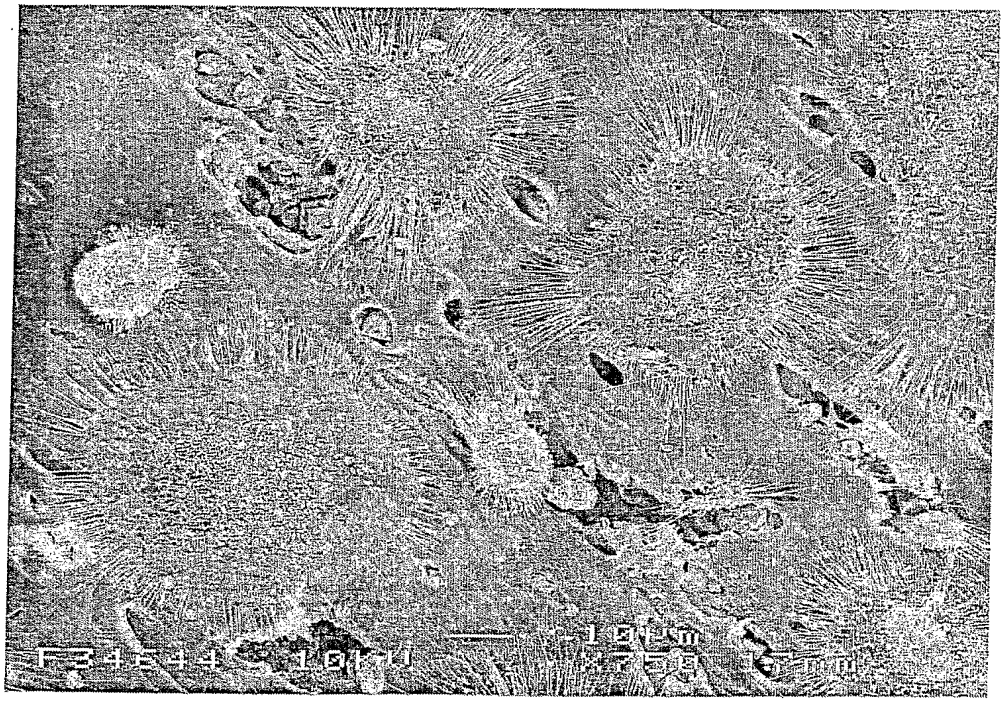
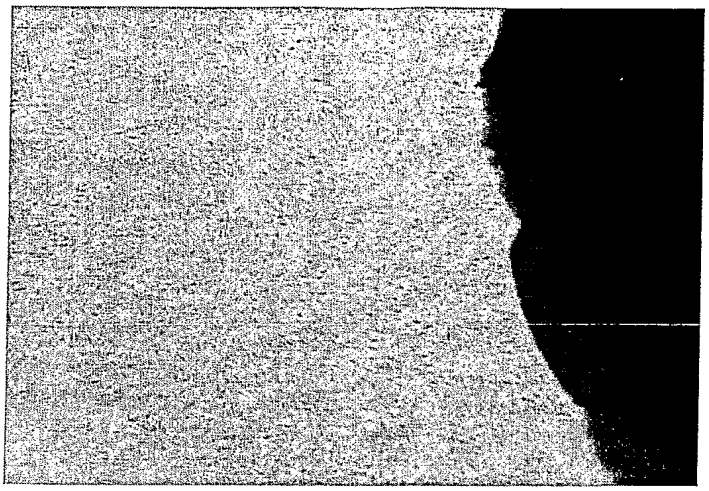
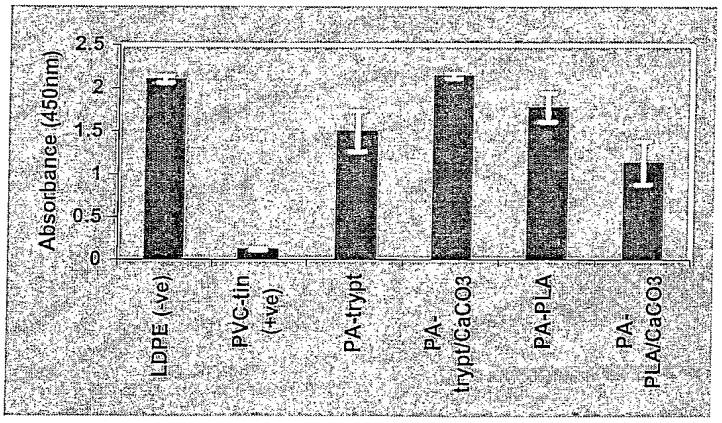


Figure 7: Osteoclast adhesion onto polyacetal (PLA/CHDM/CHDMDVE/ Trytophan diester-caprolactone)/$CaC0_3$ surface .



(8a)



(8b)

Figure 8: Bulk material cytotoxicity testing of the materials using WST test.

(8a) shows preosteoblastic MC3T3-E1, cultured around discs of polyacetal (PLA/CHDM/CHDMDVE/ Trytophan diester-caprolactone)/$CaC0_3$ indicated that the materials did not exert a gross cytotoxic effect on cells

(8b) Shows cell viability (as a function of absorbance) with a range of filled and unfilled PLA based polyacetals.